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February 10, 1998

Larry Hart, Ph.D.
Executive Secretary
Environmental Toxicology Program
National Institute of Environmental
Health Sciences
MD A3-02, P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Hart:

I am writing on behalf of Zeneca Pharmaceuticals to express our company's concerns with the National Toxicology Program's (NTP) review process for the proposed listing of tamoxifen in the *9th Report on Carcinogens*. Aside from many factual inaccuracies in the NTP's documentation serving as the agency's rationale for listing tamoxifen as a carcinogen, which this letter is intended to correct, Zeneca is very concerned about several procedural problems in the NTP's review process for substances proposed for the *9th Report on Carcinogens*. Additionally, the agency has failed to consider the public health impacts of what Zeneca and many independent scientists and patient advocates believe would be a premature and erroneous listing of tamoxifen as a substance "known" to be a human carcinogen.

Tamoxifen, which we at Zeneca produce, is widely acknowledged to be a potent weapon against breast cancer. It has a long, proven history of reducing both recurrence and mortality in breast cancer patients (*16,22,23,25*). It is credited with saving many thousands of lives yearly. Tamoxifen plays a crucial role in controlling a cancer that is expected to affect nearly one million additional women each year by the year 2000 (*15*), and the World Health Organization considers it an essential therapy for this disease (*34*). Labeling of tamoxifen as a "known human carcinogen" for endometrial cancer has, as we have seen in California and elsewhere, a clear potential to deter use of this valuable drug and add to the anxiety concerning the difficult decisions that breast cancer patients and their doctors must make, with grave public health consequences (*25,31*). Therefore, we continue to urge the NTP, and its *Report on Carcinogens* review committees, to consider with the greatest care (a) whether listing of tamoxifen as a known human carcinogen is warranted by the scientific evidence and the accepted scientific norms for evaluating human evidence for causality, and (b) the broad

role given the Secretary of HHS by Congress of advising the public and Congress on whether substances cause cancer (*2*). We urge this particularly in light of the NTP's overall mandate to act as "an extension of the Public Health Service's responsibility for safeguarding the public's health." (*28*)

The fact is, numerous scientific experts and authorities, both within and outside governmental agencies, recognize that there are substantial uncertainties in the existing data regarding tamoxifen and endometrial cancer (*6,10,12,16,20,24,27,32*). Many of those observations have been published or communicated to HHS since the February 1996 IARC evaluation. It could prove gravely misleading to the public to list tamoxifen as a substance "known" to "cause" cancer in the face of those uncertainties and in the face of notice that significant new published data concerning those uncertainties are likely to be available by 1999, when such a listing would be published, or sooner.

Professor Leslie Bernstein at the University of Southern California sent comments to the NTP Board of Scientific Counselors' RC Subcommittee in which she advised the Subcommittee not only of problems with existing human studies, but also that she and her colleagues had recently completed an NCI-sponsored case-control study, expected to be published soon, which is specifically designed to examine some of those problems (*6*). The study is designed to assess possible confounding of risk estimates by estrogen replacement therapy, oral contraceptives, and obesity. She advised that the submitted study results show that risk estimates "were dramatically modified by whether or not the woman was obese and whether or not she had previously used estrogen replacement therapy," and she suggested that the published results would show that risk of endometrial cancer was not significantly elevated when such factors were taken into account (*Id.*). Written comments by Dr. Leslie Ford of the National Cancer Institute also urged the Subcommittee to consider carefully these findings from the Bernstein study (*16*). The public discussions by the RC Subcommittee on October 30, 1997, indicated, however, that at least some Subcommittee members did not appreciate the significance of the Bernstein study.

The Bernstein study does not address all of the potential problems with previous studies. Another significant issue is likely detection (or "ascertainment") bias in those studies. Tamoxifen can cause side effects that prompt gynecological examinations that will disclose tumors at a higher rate that in unexposed control groups, thereby inflating relative risk findings. Observation of these differential effects was acknowledged by authors of the 1994 NSABP study report by Fisher et al. relied on in the *Draft Background Document*, and is evidenced by data reported from the Stockholm trial (*17*). Written comments were submitted by Dr. Lawrence Wickerham, Associate Chairman of the National Surgical Adjuvant Breast and Bowel Project ("NSABP"), advising the Subcommittee of how the ongoing Breast Cancer Prevention Trial, Protocol P-1 ("BCPT") has been designed to address this issue, and that the results of the first five-year follow-up will be available in 1999 (*33*). The NSABP recommended that HHS delay its listing decision until the results of the BCPT

study are available. Dr. Ford of the National Cancer Institute also urged the NTP to consider the results of the BCPT, as well as the Bernstein study (*16*).

In view of the above, we believe it prudent for the NTP to defer listing until such data are finalized. We further believe that it is imperative that the NTP and its reviewers appraise the data on tamoxifen and formulate their listing or no listing recommendations with the following fundamental points in mind:

Basic Points Regarding the Report on Carcinogens Review Process

1. The Federal legislation mandating the *Report on Carcinogens* listing program does not, like some other Federal statutes, require the Secretary of Health and Human Services and the NTP to review specified substances within a specified timeframe (*1*). The selection of individual substances for review is left to the Secretary. It is only after it has been finally determined by the Secretary that a substance is known or reasonably anticipated to be carcinogenic that Congress mandates that the Secretary publish a list of substances for which such determinations have been made and include that substance. Thus, it is perfectly legal and appropriate for the NTP and the Secretary to defer action on an individual substance when she has good reason to believe that new data is likely to become available in the near future which will confirm or resolve uncertainties regarding the appropriate listing determination. This is especially true in the case of a substance for which a listing determination will have a significant, predictable adverse effect on public health, thus creating a result antithetical to the broad purpose of the listing program.

2. The NTP appears to have adopted a policy that it will consider and cite only published, peer-reviewed data and articles when making decisions on listing and ranking of substances in the carcinogen review program. We are unsure as to the official source or origin for such a policy at the NTP. Nor are we aware of any legally-binding directive that would prevent the NTP and the Secretary from acknowledging pertinent research in progress, or from considering its impact on the analysis at hand, particularly when that information could help resolve uncertainties or allow the NTP to avoid scientifically inaccurate listings. The NTP solicitation of public comments on the proposed listing of tamoxifen and other substances appears to recognize that unpublished information can be submitted and considered by the NTP (*14*). For that matter, we know of no directive that would prevent the NTP and the Secretary from deciding to defer a listing determination until the findings of those studies are reported in the peer-reviewed literature where they can then be reviewed as published data.

3. The legislative history for the statute clearly reflects a Congressional intent to have the Agency distinguish carefully between substances for which the evidence of

carcinogenicity is only suggestive and those for which carcinogenicity *in humans* has been "confirmed", "clearly demonstrated", and for which the data is "convincing" (*2*). In other words, in order to be listed in the "known" category, Congress clearly intended that the supporting evidence be substantially beyond "suggestive" of a causal relationship. It is also clear from the current NTP listing criteria that a listing in the "known" category requires stronger evidence than "suggestive" evidence or that "which indicates that causal interpretation is credible," as required for a category 2 listing. As a matter of fact, the original bill designated category 2 substances as "suspected carcinogens", and this terminology was changed, and enacted as "reasonably anticipated" (*3*). This was clearly an upgrading of the evidentiary standard for category 2 beyond "suspected" and, by implication, a clear statement that category 1 listings also must be supported by substantially stronger evidence than "suspected" carcinogenicity, which would be insufficient even for listing as a category 2 substance. Despite this careful choice of language, it appears that the review committees evaluating tamoxifen are interpreting the word "indicates" (in the Agency's listing criteria for category 1) as equivalent to "suggests" rather than equivalent to "confirms", "demonstrates", or "convincingly establishes" that the substance causes cancer in humans, as would be correct (*4*).

4. The "known" listing category hinges on examining evidence from human studies to determine whether it convincingly establishes a causal relationship. This means evaluating mainly evidence from epidemiologic studies. Epidemiologists distinguish carefully between mere "association" and "causal association" (or "causal relationship"), and they employ widely-accepted principles or criteria (often referred to as the U.S. Surgeon General's or Bradford Hill criteria) for making judgments on whether the human evidence is sufficient to support a determination of causal association. This distinction, and the principles or criteria for making judgments regarding causation, appear to be very blurred or unrecognized and unutilized in the NTP review of tamoxifen to date. This is almost surely due to the scarcity of epidemiologists on the NTP review committees (*35*).

   Among the important principles or criteria for making causal judgments, as set out by the U.S. Surgeon General (*13*) and many others (*e.g., 11,26,30*), are --

   a. The consistency of the association through repeated observations in multiple and differing investigations

   b. The strength of the association across studies in terms of the relative risk ratio (an RR of less than 2.0 or 3.0 being generally considered "weak")

   c. The specificity of the association with a defined disease state or states

d. The temporality of the association (whether the disease clearly follows the exposure -- *i.e.*, effect following cause -- within a biologically reasonable period), and

e. The coherence of the association with human biological and surveillance data

Other criteria often invoked and examined include whether the data evidence a "biological gradient" (or "dose-response" -- sometimes considered an aspect of "coherence" and "strength"), and whether the relationship is "biologically plausible" (a variation on the "coherence" criterion).

Application of these criteria is important to ensure the scientific accuracy of the NTP listings. However, from the NTP written and oral presentations, as well as from the composition of the review committees and statements made by individual committee members, it seems that the analysis to date has not rigorously applied these commonly-accepted criteria. As other examiners have noted, and as discussed further below, the human evidence as a whole falls far short of establishing a causal relationship for numerous reasons. These reasons include --

-- a clear lack of consistency across the body of epidemiologic studies, with the effect of a large body of negative, null, or statistically insignificant findings given little or no weight

-- even among the studies with positive findings, lack of strength in the relative risk findings; and even when they appear strong, as in the Fisher et al. study, the findings have, upon further review, been found to be weak (*12*)

-- substantial uncertainty regarding temporality due to likelihood of detection bias resulting from unmasking of pre-existing or synchronous tumors due to more careful examination of study subjects receiving tamoxifen than the control groups

-- lack of coherence in human biological data due to tamoxifen also being recognized as effective in treating endometrial cancer, and in surveillance data due to the apparent lack of elevation in incidence in study findings above normal population incidence

5. The principles or criteria for causality discussed above are most commonly used to evaluate the evidence from a body of studies, although they have more limited application in evaluating individual studies. In addition to examining the total body of

studies with those principles or criteria, those evaluating the evidence must also, however, consider the quality of the individual studies, and particularly whether their results could have been due to bias, confounding, or chance (*11,13,26,30.*). The probative value of various individual positive tamoxifen studies is limited by a failure or inability to rule out one or more clinically relevant potential sources of confounding or bias. Further, as discussed below, the manner of data collection and analysis artificially inflated some of the risk estimates reported from the studies. Although these limitations were often acknowledged by the study authors themselves, the NTP committee comments and recommendations were conclusory and dismissive regarding such concerns.

The NTP listing criteria specifically require that substances be listed no higher than the "reasonably anticipated" category if "causal interpretation is credible, but that alternative explanations such as chance, bias, or confounding, could not adequately be excluded...." The criteria thus place an affirmative burden on the NTP and the Secretary to ensure that alternative explanations have been adequately explored and ruled out. The record of NTP review does not reflect this thoroughness, and a more cautious and highly critical analysis of these factors should be of particular priority to the NTP and its committees.

6. Listing as a "known" human carcinogen requires that the listing be based on evidence "from studies in humans which indicates a causal relationship...." While the RC listing summary at the beginning of the *Draft Background Document* contains a statement to this effect, the summary then asserts that its conclusion regarding tamoxifen is supported by evidence from experimental animal studies and mechanistic data, including *in vitro* data. It appears that NTP officials and reviewers may be under the impression that it is permissible to consider such non-human evidence in support of a category 1 ("known") listing. The likelihood of this appears high particularly in view of the weakness of the evidence from human studies, as discussed above. If the reviewers have been operating under such an assumption, we believe it can be shown conclusively that such a view is erroneous and would invalidate the listing decision. Only "evidence from human studies" should be discussed in connection with possible listing in the "known" category; if evidence from non-human studies is to be considered, it must be in connection with the "reasonably anticipated" category or a recommendation or decision not to list. The *Draft Background Document* should reflect this distinction.

7. At the October 30-31 listing review meeting, RC Subcommittee members indicated that they thought the Subcommittee was confined to a very limited role: voting "Yes" or "No" on the views and recommended listings set forth by the RG1 and RG2 committees and contained in the *Draft Background Document.* The basis for this belief is unclear; we are not aware of any written "charge" to the Subcommittee or

other reviewers which so restricts their scientific judgment and recommendations. The NTP's documents describing the listing review process are broadly worded rather than restrictive. Additionally, if the issue raised for the review groups is simply whether to list, as was the case with tamoxifen in the July 11, 1997, *Federal Register* notice (*14*), then the RC Subcommittee and the other reviewers should be able to go beyond voting simply "Yes" or "No" on a category 1 listing and recommend deferral of a listing decision, no listing, or listing in category 2.

8. The *Report on Carcinogens* review process is not delimited by the legislation. It appears that Departmental policy states that certain committees will be included in the review process, but the process anticipated by the legislation does not exclude the possibility of additional review entities. Therefore, we believe there exists a great deal of discretion to modify or supplement the process at any time, for any specific substance, where the Secretary or her delegatees determine that this would further the broad goals of the program. In this instance, it appears necessary and appropriate to convene an additional blue-ribbon panel whose membership includes a substantial number of experts with strong credentials in reproductive epidemiology and gynecology relevant to the issues under consideration.

More Specific Points Regarding the NTP Review of Tamoxifen to Date

It is also fundamental that the scientific data or commentary on tamoxifen (or any other substance undergoing NTP review) must be presented fully, fairly, and accurately. The *Draft Background Document for Tamoxifen* contains a number of inaccuracies, omissions, and deficiencies that should be corrected:

1. The *Draft Background Document* listing summary (RC-1 to RC-2) states that Professor MacMahon concluded that the studies were "suggestive of a causal association ... but were not conclusive because of confounding . . . ." (Emphasis added) This statement is inaccurate. Professor MacMahon did not conclude that the evidence suggests a causal association; he concluded that the studies "suggest that an association . . . exists." (*27, emphasis added*). The distinction between causal association and simple association is important and widely recognized, as noted above. It is noteworthy that Professor MacMahon (an eminent breast cancer researcher), sub-titled his article "Perspectives of an Epidemiologist". After the above statement, he went on to state that even the evidence of an "association" was "far from conclusive" and "incomplete", and that "legitimate questions can still be raised about the relationship . . . and particularly about whether the relationship, if real, is a causal one." (*At 136, emphasis added*). Professor MacMahon should be quoted fully and accurately in the *Draft Background Document*, and attention should be drawn to the essential distinction between "association" or "suggested association" and a known "causal relationship".

2. The *Draft Background Document* omits discussion or reference to other peer-reviewed articles which, like Dr. MacMahon's, have been published since the 1996 IARC review and point out the serious problems with existing human studies, the insufficiency of the evidence to support a causal inference, and the lack of relevance of the animal and *in vitro* data (*8,10,12,15,20*).

3. One of the most prominent issues raised by Professor MacMahon (among others) is that it is likely that use of unopposed hormone replacement therapy ("HRT") by study subjects has confounded many of the human studies on tamoxifen. The NTP, in its summary of the *Draft Background Document* (section entitled "Other Information..."), does recognize that it has been demonstrated that such HRT exposures pose "a highly elevated risk for endometrial cancer". However, we note that the significance of this observation is far more central to the analysis of the tamoxifen human evidence than placement in the "other information" section would suggest. This acknowledgment of potential for substantial confounding belongs in the first section of the summary where the human studies are discussed, with an explanation that substantial confounding by unopposed HRT, as suggested by Professors MacMahon, Bernstein, and others, remains a distinct possibility despite IARC's unexplained dismissal of the issue.

4. The *Draft Background Document* summary omits any mention of the fact that tamoxifen has been identified by the World Health Organization since 1994 as the only pharmaceutical essential to the treatment of endometrial cancer (*34*). This WHO recognition was based upon an extensive body of human evidence. The 1996 IARC monograph review of tamoxifen very briefly noted only a few such studies, did not reference the WHO finding, and did not discuss the significance of this information. More recent reviews continue to confirm WHO's 1994 finding (*10,12,19*). And this evidence from human studies is directly pertinent to the major causality criteria of "consistency" and "coherence" among human studies. As Dr. Carmel Cohen of Mt. Sinai School of Medicine recently observed after reviewing such data, "it is difficult to reconcile this tamoxifen effect with the notion that it is a drug that initiates and promotes the replication of endometrial cancer, for clearly it has a therapeutic role in this disease." (*10*) This point also suggests that the *Draft Background Document* is mistaken in stating that tamoxifen is likely to have the same effect as conjugated estrogens in the human uterus.

5. The *Draft Background Document* should acknowledge that the effect of detection (or "ascertainment") bias has not been explored in existing published studies, that clinical trials data suggest this effect, and that studies are now under way to evaluate it (*e.g.*, the BCPT, discussed above). The issue of detection bias is highly significant, and it coincides with the causation criterion of "temporality", which is the one criterion that

is absolutely essential to a finding of cause-effect relationship. That is, if the cancer existed undetected prior to the use of tamoxifen, the effect cannot have followed the putative cause, and the causal criterion of "temporality" is not satisfied. The likelihood of such bias is further supported by point 6, below.

6. The *Draft Background Document* should inform the reviewers that the incidence of endometrial cancer observed in breast cancer patients treated with tamoxifen is virtually the same as seen with routine screening for endometrial cancer, as noted by Dr. Jordan of the Robert H. Lurie Cancer Center in his written comments to the RC Subcommittee (*24*). The *Draft Background Document* should also explain the significance of this point with regard to the issue of potential detection bias and the effect it would have on apparent positive study findings to date.

7. The *Draft Background Document* places particular emphasis on three studies that are all either substantially flawed or given unwarranted weight:

   -- The Curtis et al. 1996 cohort study is described as having found a statistically significant elevation in the risk of endometrial cancer "in women who had received tamoxifen therapy". As Professor Bernstein explained in her written comments to the Subcommittee, based on her intimate experience with NCI SEER data it is clear that the Curtis study used SEER registry information that was unclear as to whether women were exposed or unexposed specifically to tamoxifen. Such women may not have received the antiestrogen tamoxifen, may have been exposed to another hormonal therapy, or may not have received any medication that interrupted or altered the patient's hormonal status (*6*).

   -- The two key clinical trials (among fourteen) that showed a statistically significant elevation in risk (Fisher et al. 1994 and Rutqvist et al. 1995) are described by the NTP as "strong". However, as Dr. MacMahon noted in his review, the number of endometrial cancers in the control groups for both studies were unexpectedly low, which would have had the effect of artificially inflating the findings (*27*). Additionally, some clinical studies used control groups drawn from the general female population, when such a comparison is not appropriate because breast cancer itself has been shown to be associated with an increase in endometrial cancer (RR of 1.72,*5*). Like others, Dr. Creasman has examined the data from the Fisher et al. study and concluded there are sound reasons for concluding that the findings were either not positive or only weakly positive (RR of 1.0 to 1.7 rather than 7.5 (*12*). Such studies cannot be described as containing "strong" findings when there are identifiable problems with the representativeness of the control groups and classification of cases, and the *Draft Background Document* should contain this point.

8. The *Draft Background Document* acknowledges the lack of positive findings in the other twelve clinical studies, but it dismisses those findings with the observation that their combined results shows 29 cases of endometrial cancer in patients receiving tamoxifen versus 14 in controls. Such arithmetical "combining" to obtain a summary number without regard for careful qualitative analysis of the individual studies, discussion of variations in individual study outcomes, or exploration of uncertainties and assumptions, is a controversial approach and is likely to amplify biases and/or confounding that were present in individual studies (*7*). There should be a fuller explanation and justification of such an approach in the *Draft Background Document*, or else the "combining" approach results should be removed.

9. The summary portion of the *Draft Background Document* states that in the study by Cook et al. (1995) "no increase [in risk] was seen . . . ." To be accurate, it should state that the study actually found a <u>decrease</u> in the incidence of endometrial cancer in tamoxifen-treated women.

10. With regard to animal data, the *Draft Background Document* states that they "also provide evidence of tamoxifen's carcinogenic effects." This statement is very misleading, suggesting that tamoxifen has been shown to induce endometrial cancer in animals. All of the appropriately conducted animal experiments have shown that tamoxifen is associated with no increase in endometrial cancer in laboratory animals. Only two studies could be considered even remotely supportive of the statement in the *Draft Background Document*. One of those was conducted on neonatal mice, which do not provide a sound model for inferring similar effects in humans. The second such experiment (on rats) used a non-standard protocol and has not been reproduced and validated. These important qualifications should be explicit in the *Draft Background Document*, and it should be acknowledged that the animal data demonstrate a complete lack of predictiveness of adverse health effects in humans (*20*).

11. The statement in the "Other Information . . ." portion of the summary portion of the *Draft Background Document* that "tamoxifen would likely produce the same effects as conjugated estrogens in the uterus" (*i.e.*, increases in endometrial cancer) is simply wrong. Recent data show that tamoxifen produces effects on the human uterus different from those of estrogen (*10,12*). These data are consistent with the data showing the value of tamoxifen for <u>treating</u> endometrial cancer. It should be noted that much of the data were not available at the time of the February 1996 IARC review.

12. The *Draft Background Document* should openly acknowledge, as do the authors of the study, that the findings of Hemminki et al. with regard to DNA adducts in human tissue have not been found by other investigators (*10,11*), and that Hemminki et al.

acknowledged in their work that they could not be certain from their data that the adducts they observed were actually attributable to endometrial tissue (*21*).

Actions Requested

1. We request that changes in accordance with the above observations be made to the review presentations and record.

2. We request that NTP terminate its current review of tamoxifen and defer further review until consideration of the *Tenth Report on Carcinogens*. With so much at stake in terms of the potential public health consequences of its listing action, the NTP should exercise great caution in view of the serious issues regarding uncertainties that have been raised and the likely availability of significant data to confirm or resolve those uncertainties by the time reviews for the *Tenth Report* commence in 1999.

Sincerely,

Gerard T. Kennealey, M.D.
Vice President, Medical Affairs

cc: Dr. C. W. Jameson
Members of the NTP Executive Committee
Members of NTP Board of Scientific Counselors and
its RC Subcommittee

REFERENCES AND NOTES

1. For example, sec. 112 of the Clean Air Act, 42 USC 7412, contains a list of substances and sets out specific timeframes within which EPA must act to regulate those substances.

2. H.R.Rep. No. 95, 95th Cong., 2d Sess. at 28 (May 15, 1978); Cong. Rec. H-34938 (Oct. 10, 1978). The legislative provisions came from the House bill and the House-Senate conference; there were no relevant provisions in the Senate bill.

3. The House bill mandated publication of a list of "known or suspected carcinogens", while the final Act changed this to "are known to be carcinogens or may reasonably be anticipated to be carcinogens. . . ." Compare sec. 306(c)(10) of H.R. 12347 as reported in H.R. Rep. No. 95, *supra* n. 2, with 42 USC 241(b)(4), and see the Joint House-Senate Summary and Explanation, 124 Cong.Rec. H13566, Oct. 14, 1978.

4. In this connection, it should also be noted that the plain language of the legislation appears to indicate that Congress did not intend that the Secretary and the NTP would review pharmaceuticals. The statute directs the Agency to review the "effluent, ambient, or exposure standard" established by a Federal agency for each substance reviewed, and the extent to which such standard "decreases the risk to public health from exposure to the substance. . . ." This language appears to be aimed at involuntary exposures from substances in media such as air, water, soil, and food, rather than pharmaceuticals administered under medical supervision, and could be so interpreted by the agency. If Congress had intended to cover pharmaceuticals, it would have likely used the term "dose".

5. Adami H-O, "On the age-dependent association between cancer of the breast and of the endometrium, a national cohort study", *Brit. J. Canc.* 55:77-80 (1987).

6. Bernstein L (USC/Norris Comprehensive Cancer Center), letter dated Oct. 23, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens.*

7. Blair et al., "Guidelines for application of meta-analysis in environmental epidemiology", *Reg. Tox. and Pharm.* 22:189-97 (1995).

8. Carmichael et al., "Lack of genotoxicity of tamoxifen in the human endometrium", *Canc. Res.* 56:1475-79 (1996).

9. Carmichael et al., "A lack of evidence for tamoxifen- or toremifene-derived DNA adducts in the human endometrium", abstract of poster presentation for the 1998 annual meeting of the Amer. Ass'n of Canc. Res. (1997).

10. Cohen CJ, "Tamoxifen and endometrial cancer: Tamoxifen effects on the human female genital tract", *Semin. Oncol.* 24(1)(Supp. 1):55-64 (1997).

11. Cole P, "Causality in Epidemiology, Health Policy, and Law", *Env. Law Rep.* 27(6):10279-85 (1997).

12. Creasman WT, "Endometrial cancer: Incidence, prognostic factors, diagnosis and treatment", *Semin. Oncol.* 25(1)(Supp. 1):140-50 (1997).

13. Department of Health and Human Services, "The health consequences of smoking -- cancer, a report of the Surgeon General" (1982).

14. Department of Health and Human Services, notice soliciting public comments for proposed listings or delistings in the 9th Report on Carcinogens, 62 *Fed.Reg.* 37272-73 (July 11, 1997).

15. Forbes JF, "The Control of Breast Cancer: The Role of Tamoxifen", *Semin. Oncol.* 24(1)(Supp. 1):5-19 (1997).

16. Ford LG (National Cancer Institute), letter dated Oct. 23, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*, and attached letter dated October 30, 1995, to Ms. Catherine Caraway of the California Office of Env. Health Haz. Assess.

17. Fornander et al., "Adjuvant tamoxifen in early-stage breast cancer: effects on intercurrent morbidity and mortality", *J. Clin. Oncol.* 9:1740-48 (1991).

18. Fornander et al., "Effects of tamoxifen on the female genital tract", *Annals N.Y. Acad. of Sc.* 622:469-76 (1991).

19. Gelman EP, "Tamoxifen for the treatment of malignancies other than breast and endometrial carcinoma", *Semin. Oncol.* 24(1)(Supp. 1):65-70 (1997).

20. Guzelian PS, "Relevance of rat liver tumors to human hepatic and endometrial cancer", *Semin. Oncol.* 24(1)(Supp. 1):105-21 (1997).

21. Hemminki K, et al., "Tamoxifen-induced DNA adducts in leucocytes of breast cancer patients", *Carcinogenesis* 18:9-13 (1997).

22. International Agency for Research on Cancer, press release, "IARC evaluates carcinogenic risk associated with tamoxifen" (Feb. 1996).

23. International Agency for Research on Cancer, "Tamoxifen", *IARC Monographs on the Eval. of Carc. Risks to Humans* 66:253-365 (1996).

24. Jordan VC (Northwestern Univ. Med. Sch.), letter dated Oct. 22, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

25. Langer AS (Natl. Alliance of Breast Cancer Organizations), letter dated Oct. 29, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

26. Lilienfeld DE and Stolley PD, *Foundations of Epidemiology* 263-67 (3d ed. 1994, Oxford Univ. Press).

27. MacMahon B, "Overview of studies on endometrial cancer and other types of cancer in humans: Perspectives of an epidemiologist", *Semin. Oncol.* 24(1)(Supp. 1):122-39 (1997).

28. National Institutes of Health, "The National Toxicology Program, OVERVIEW: Current Directions and Evolving Strategies", public information brochure (1998).

29. NIEHS/National Toxicology Program, "Draft Background Document for Tamoxifen, September 29, 1997".

30. Schlesselman JJ, "`Proof' of Cause and Effect in Epidemiologic Studies: Criteria for Judgment", and references therein, *Prev. Med.* 16:195-210 (1987).

31. Steinberg M (Zeneca Pharmaceuticals), letter dated Oct. 24, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

32. "Tamoxifen & The Uterus: Potential Uterine Risks of Anti-Oestrogens" International Meeting Organized by: The Flemish Work Group Gynecological Oncology and the Dept. of Obstetrics & Gynecology of Algemenene Kliniek, St-Jan Brussels, December

12-13, 1997. The consensus during this meeting was that the data, including new data presented at the meeting, are sufficient only to indicate an association, not a causal relationship. The abstracts from the meeting will be published in the near future in a supplement of *The European Journal of Cancer*.

33. Wickerham DL (Natl Surgical Adjuvant Breast and Bowel Program), letter dated Oct. 23, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

34. World Health Organization, "Essential drugs for cancer chemotherapy", *WHO Bull.* 72(5):693-98 (1994).

35. The legislative history of the law requiring the *Report on Carcinogens* does not reflect a Congressional intent to give leadership of the program to the National Institute of Environmental Health Sciences or the National Toxicology Program (administered by NIEHS). While the final Joint House-Senate Summary and Explanation (see note 3, above) indicates that the NTP was expected to play a major role, the Congressional delegation is to the Secretary, and the Summary and Explanation indicates appears to give at least as much emphasis, if not more, to the roles of the National Cancer Institute and the Food and Drug Administration. This makes sense because listings in the "known" category require epidemiologic expertise, and the scientific expertise of the NTP is primarily in the conduct and interpretation of animal experiments, while NCI and FDA have more experience with human studies.